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PRINCIPAL INVESTIGATOR: Michael V. Seiden, M.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, MA 02114

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13. ABSTRACT (Maximum 200 Words)

This Award funded the initiation of a mentored research experience in ovarian cancer biology at the Dana Farber/Harvard Cancer Center. The primary aims, articulated in the Statement of Work, included creating a mechanism to identify and select outstanding postdoctoral fellows who had a commitment to serous multi-year experience in research that was directly related to a topic in or immediately applicable to ovarian cancer. The second aim was to provide a mentored experience for selected fellows. The third aim specified the delivery of feedback to the trainees by mentors and the program PI. The final aim described a rigorous review process for the program. These aims are all being addressed. The program has selected 3 talented senior post doctoral fellows who are all assigned to work with Professors at Harvard Medical School in the fields of Medicine/Oncogenesis, Surgery/Signal transduction, and Cell Biology/Signal transduction. These fellows conduct their research at 3 different institutions within the Dana Farber/Harvard Cancer Center. All the fellows are productive in their research and one has already successfully competed for a faculty development grant. Formal review of the program is planned latter this spring as is the second round of competition for fellows.

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Ovarian Cancer Training Program at the DF/HCC

Introduction

The purpose of this proposal was to create an ovarian cancer training program that was designed to expose postdoctoral fellows to a mentored research environment in various fields of biology. Specific research projects were to be focused on problems relevant to ovarian cancer biology. The program has been successful in identifying three postdoctoral fellows who were placed in highly successful laboratories of molecular oncology, cell biology, and signal transduction. These individuals have all begun a successful period of research with mentoring. In addition all have participated and presented in and ovarian cancer research seminar series focused entirely on ovarian cancer biology. Two of the fellows are continuing their research experience for a second year with grant support due to their success and positive reports from their mentors. The third fellow has received junior faculty funding from the Ovarian Cancer Research Foundation and will successfully transition off this training grant.

The statement of work for this proposal included four goals or specific aims.

- Identify and select outstanding postdoctoral candidates for participation in ovarian cancer training program
- Identify appropriate faculty and mentors for selected postdoctoral fellows
- Review progress of postdoctoral candidates with principal investigator and executive committee
- Review the overall training program

Each of these aims had several sub aims, which will be discussed further below. These made excellent progress on accomplishing most of these aims.

Specific Aim I

- **Identify and select outstanding postdoctoral fellows.** This aim included identifying highly qualified individuals who are interested in a focused and mentored research experience in ovarian cancer biology. Included within the statement of work was the solicitation of applicants from training clinical program faculty as well as Cancer Center Leadership and Harvard Medical School leadership. In addition, the fellowship program was advertised in journals. In March 2003 advertisements were placed in Gynecologic Oncology, Journal of Clinical Oncology and Cancer Research. In addition letters were sent to the Medical Oncology, Radiation Oncology, Gynecologic Oncology and Cancer Center Fellowship Directors and Leaders in the Dana Farber Harvard Cancer Center. Finally, a list of approximately sixty ovarian cancer leaders were contacted including medical oncologists, gynecologic oncologists and Cancer Center Directors at institutions such as Memorial Sloan Kettering, Cleveland Clinic, Fox Chase Cancer Center, Duke, University of Mississippi, M.D. Anderson and many others. We received initial inquiries from approximately 25 candidates and 12 candidates submitted formal applications. These were reviewed by the executive committee and given scores. The three fellows receiving the highest rank all accepted positions within the fellowship. These fellows included:
- **Ronny Isaac Drapkin** – Dr. Drapkin is an MD, PhD from the University of New Jersey, New Brunswick where his research included important work on transcription control with Dr. Reinberg. Dr. Drapkin's prior work included three publications in Nature, two publications in the Proceedings of the National Academy of Science as well as additional publications in

the Journal of Biologic Chemistry, and Molecular and Cellular Biology. He subsequently was accepted to and completed a residency in anatomic pathology at the Brigham and Women's Hospital and entered the laboratory of Dr. David Livingston (see mentors below). Dr. Drapkin's work includes identifying and validating disease related RNA and protein expression in early ovarian carcinoma with most of his work focusing on the molecule HE4 an acidic whey protein. He has also been working on an in vivo system to study the pathogenesis of ovarian cancer using a BRCA-1 knock out murine model. Finally, he's also studying the role of BACH 1, and BRCA-1 associated protein. (See the attached CV in appendix 1)

- **Sanja Sale, MD** – Dr. Sale received her undergraduate and medical degree from the Zagreb School of Medicine in Zagreb, Croatia. She completed her first postdoctoral fellowship at Karl Franzens University in Graz, Austria and a second postdoctoral fellowship at Stanford University School of Medicine with Branimir Sikic. In Dr. Sikic's laboratory she looked at genetic variations and beta tubulin and the potential role of tubulin mutations in generating taxane resistance in epithelial ovarian cancer. She also looked at other issues related to paclitaxel drug resistance including transcriptional regulation of the MDR-1 gene once again focusing predominantly on ovarian tumors. At the initiation of this fellowship program she was joining the laboratory of John Blenis, Professor of Cell Biology (see mentors below) where she is working on the role of a PI3K/Akt pathway and the Ras/MAPK signaling pathway in 3D ovarian organoid cultures. She is working on state of the art technologies to measure activation of these pathways in 3D cultures and using siRNA technology to evaluate the effects of disruption of these pathways in three-dimensional cultures. (See Appendix 1).
- **Yong Zhan, PhD** – Dr. Zhan received his medical degree at Chinese Medical University and in 1996 through 2000 was on the faculty in China. He came to the United States in 2000 to begin his U.S. based research career in molecular medicine at the University of Massachusetts. There he worked on intracellular targets of NADPH oxidation biochemistry associated with AKT activation. At the University of Massachusetts he had publications in the Journal of Biological Chemistry and in the Proceedings of the National Academy of Science. His current research is in the laboratory of Dr. Patricia Donahoe (see mentors below). With Dr. Donahoe he is working on identification of the type I receptor for mullerian inhibiting substance. Mullerian inhibiting substance is a molecule important in the development of the female reproductive tract. Recent research, done in Dr. Donahoe's laboratory, has demonstrated that approximately 50% of ovarian carcinomas express the MIS receptor and their growth can be inhibited by the addition of MIS. Dr. Donahoe's laboratory has identified the ligand and the type II receptor which heterodimerizes with the type I receptor. The specific type I receptor that heterodimerization with the type II receptor has not been fully characterized in ovarian cancer. Dr. Zhan is looking to confirm the identity of the type I receptor to also work on the downstream signaling of the MIS heterotrimeric receptor. (Dr. Zhan's CV is attached in Appendix 1)

Specific Aim II

- **Identifying appropriate faculty and mentors for selected postdoctoral fellows.** The main purpose of this aim was to insure that fellows were associated with appropriate faculty and that additional mentors be associated with the fellow. Primary mentors for each of the fellows are all Professors at Harvard Medical School. Two of these mentors are members of the National Academy of Science. Bio-sketches of the primary mentors for Drs.: Drapkin (Dr. Dave Livingston) Sanja Sale (Dr. John Blenis) and Yong Zhan (Dr. Patricia Donahoe) are enclosed in Appendix 2. Drs. Livingston and Donahoe were identified as members of the Ovarian Cancer Training Program Faculty during the grant submission. Dr. Blenis has been

added to the faculty roster (Appendix 2), as has been Dr. Sandra Orsulic (See Appendix 3 for biosketch).

- John Blenis has been a Professor In Cell Biology at Harvard Medical School since 1996 and is a recipient of the NIH/NCI Merit Award looking at mitogenic and oncogenic regulation of ERK/RSK signaling. He has over 100 publications with several dozen in prominent journals such as Cell, Nature, MCB and JBC all focusing on signal transduction through important signal pathways involved in oncogenesis.

- Dr. Orsulic was recruited onto the faculty after the training grant was submitted. She has developed one of the first molecularly defined mouse models for epithelial ovarian cancer while completing her senior postdoctoral fellowship with Dr. Harold Varmis at the NIH and subsequently at Memorial Sloan Kettering.

Additional Mentees:

- Dr. Drapkin has identified an additional mentor Dr. Steven Skates who is working with him to design models and validate HE4 in early ovarian cancer and other markers in identifying early stage ovarian carcinoma. Dr. Sanja Sale has received advice and mentoring both from Dr. Joan Brugge and from Sandra Orsulic. Dr. Zhan still needs to identify a third mentor which will be accomplished in the next three or four months.

Specific Aim III

- **Review the progress of postdoctoral candidates by the principal investigator, mentors, and the executive committee.** Each of the trainees has presented their research formerly at the monthly ovarian cancer research meeting now directed by Dr. Sandra Orsulic. The list of speakers and topics is included in Appendix 4. In addition, each of these mentors has provided written feedback to the program P.I. on their mentees, which is included in Appendix 5. Confidential feedback from the mentees of their mentors has also been collected. Since all three fellows demonstrated enthusiasm, progress in their primary project and strong support from their mentors all have been offered support for a second year of funding. Drs. Zhan and Sales accepted this funding. Dr. Drapkin received faculty development funding from the Ovarian Cancer Research Foundation and will come off the training grant. We will compete this position this spring. Training support for Drs. Sale and Zahn will be limited to two years of funding and those positions will be re-competed both internally and nationally in the spring of 2006.

Specific Aim IV

- **Review overall training program.** The first annual review of the training program is scheduled for May 2005 and hence has not yet occurred. Each of the members of the executive committee will receive a copy of this overview.

  In addition, the training program was designed to synergize with other training opportunities. Since submission of this grant, the Dana Farber Harvard Cancer Center was awarded the DF/HCC Ovarian SPORE grant. Funding for this program is due to begin in the summer of 2004. The SPORE program includes a career development program for which Dr. Seiden serves as the P.I. The career development program will serve to fund junior faculty and it is possible that candidates supported on the current

training program might receive additional support through the SPORE Program. In addition, the DOD funding is only three years in duration and hence, in the spring of 2006 Dr. Seiden will be applying for continued funding of the Ovarian Cancer Biology Program through the NCI-based T32 mechanism.

Key Research Accomplishments and Reportable Outcomes:

This grant was funded as of the spring of 2003 with the selection of fellows to initiate funded research in July 2003. At this point the research fellows had approximately nine months of funded research.

Key accomplishment for the program have included:

- Selection of three highly qualified postdoctoral fellows for training.
- Establishment of an ovarian cancer research didactic course
- Formal review of mentees progress through oral presentation
- Formal review of research progress by mentees with feedback.
- Funding of the Ovarian Cancer SPORE grant, which includes a training program that will synergize with the current Department of Defense Award.

Publications by research fellows since initiating this award are still limited.

- Ronald Drapkin –
  - 1) Cantor S*, Drapkin R*, Zhang F, Lin Y, Han J, Pamidi S, Livingston DM. The BRCA1-associated protein BACH1 is a DNA helicase targeted by clinically relevant inactivating mutations. Proc Natl Acad Sci 2004; 101: 2357-2362. * *denoted equal contribution.*
  - 2) Drapkin R, Crum CP, Hecht J. Expression of candidate tumor markers in ovarian carcinoma and benign ovary: evidence for a link between epithelial phenotype and neoplasia. *Submitted to Human Pathology*
- Sanja Sale – none
- Yong Zhan - none

In addition fellows have been encouraged to apply for supplemental awards. Recently Dr. Drapkin has received the individual investigator award from the Ovarian Cancer Research Foundation. Drs. Zhan and Sale have not yet applied for additional research funding.

Conclusion:

The Dana Farber Harvard Cancer Center Training Program has started on schedule and has identified three highly qualified trainees who have been assigned to nationally recognized scientists. One of the trainees has successfully competed for a faculty transition award and the other two remain very productively involved in the research program. Didactics in mentoring has also begun including written feedback to the candidates. The recent award of the NCI sponsored Specialized Program Of Research Excellence (SPORE) to the Ovarian Cancer Program at the Dana Farber Harvard Cancer Center will augment this training program in the next two years.

Appendices

Appendix I - Mentees CV's

Appendix 2- Biosketches: Livingston, Blenis, Donahoe,
Appendix 3- Biosketch Dr. Orsulic
Appendix 4- List of Speakers/Topics
Appendix 5- Mentors feedback

CURRICULUM VITAE

Part I: General Information

DATE PREPARED: January 14, 2004

Name: Ronny Isaac Drapkin

Office Address: Department of Pathology, Brigham and Women's Hospital, Department of Cancer Biology, Dana Farber Cancer Institute, 1 Jimmy Fund Way, Boston, MA 02115

Home Address: 44 Melbourne Avenue, Newton, MA 02460

Email: ronny_drapkin@dfci.harvard.edu **FAX:** (617) 632-4381

Place of Birth: Valdivia, Chile

Education:

1990	B.A.	Brandeis University (Biochemistry), Waltham, MA
1996	Ph.D.	University of Medicine and Dentistry of New Jersey, New Brunswick, NJ
1998	M.D.	University of Medicine and Dentistry of New Jersey

Postdoctoral Training:

Internships and Residencies:

1998-2002 Resident in Anatomic Pathology, Brigham and Women's Hospital

Clinical and Research Fellowships:

2000- Postdoctoral Research Fellowship, Department of Cancer Biology, Dana Farber Cancer Institute

Licensure and Certification:

2001- Massachusetts Board of Registration in Medicine License #209348

Academic Appointments:

1998-2002	Clinical Fellow in Pathology, Harvard Medical School, Boston, MA
2002-	Instructor in Pathology, Harvard Medical School, Boston, MA

Professional Societies:

1990- American Medical Association Member

1991-1995	Medical Society of New Jersey	Representative to Board of Trustees
1998-	Massachusetts Medical Society	Alternate Delegate of Resident Section
1998-	American Society of Clinical Path	Junior Member
1998-	College of American Pathologists	Junior Member

Awards and Honors:

1988	William Mazer Research Fellowship Award
1990	Richter Award for Research Excellence
1990	Combined Medical Scientist Fellowship Program
1991	UMDNJ Research Fellowship Award
1992	Syracuse University Clinical Medical Fellowship Award
1994-95	NIH Training Grant in Molecular and Cellular Biology

Part II: Research, Teaching, and Clinical Contributions

A. Narrative report of Research, Teaching and Clinical Contributions

Research: Ovarian cancer is the most lethal of the gynecological malignancies, yet the morphologic progression and molecular pathways involved in its pathogenesis are poorly understood. The lack of symptoms early in the disease course, as well as the absence of a sensitive and specific screening test for early disease detection explains why seventy-five per cent of epithelial ovarian cancers (EOC) are diagnosed at advanced stages. The field of functional genomics has advanced our knowledge of genes expressed in EOCs but it has done little to improve our understanding of the molecular pathways involved in these tumors. Therefore, there is an urgent need to discover ways to diagnose ovarian cancer at an early stage. My research focuses on developing an vivo imaging system for early ovarian cancer in the mouse model. The initial approach has been to isolate promoters of markers up-regulated during human and murine ovarian tumor cell development and generate transgenic mice harboring a luciferase-green fluorescent protein fusion cDNA under the control of these promoters. My preliminary results have identified four candidate tumor markers whose promoters may be suitable. The transgenic mice will be crossed to mice harboring mutations in the BRCA1 and p53 tumor suppressor genes. These mutations predispose the mice to developing ovarian and breast cancer. The hope is that the progeny mice will carry a transgene that is activated during the process of neoplastic transformation in the ovary, resulting in the production of bioluminescent tumor cells that can be imaged in the living mouse, in real-time, by the Xenogen IVIS™. Development of an animal model capable of detecting small numbers of light producing tumor cells offers the hope of deciphering the early steps in ovarian carcinogenesis. Such a model could lead to further insights that have implications for the development of new early diagnosis and treatment strategies in humans.

Teaching: My current teaching contributions include serving as a laboratory instructor for the first year medical school course in Pathology (HST-030) and the second year course in Pathology (IN714.0).

Clinical: I currently serve on the Autopsy Service at the Brigham and Women's Hospital one month per year.

B. Funding Information

2000-2003 Department of Pathology (BWH) NIH Training Grant T32-HL07627
2003-2005 Ovarian Cancer Research Program Grant from DFHCC
2004-2005 Individual Investigator Award from the Ovarian Cancer Research Fund, Inc.

C. Report of Current Research Activities

1) In vivo and in situ molecular probing of developing ovarian cancer, Instructor
2) Biochemistry and genetics of BRCA1 associated proteins (BACH1), Instructor

D. Report of Teaching

1. Local Contributions
   a. Harvard Medical School courses:

Years taught: 1999-present
Course: HST 030 Human Pathology
Role: Laboratory and Small Group Instructor
Students: First Year Medical Students and MIT Engineering Students
Time: Three-month course in the Fall; 2 days per week; one hour preparation and 2 hours teaching per session

Years taught: 1999-present
Course: HMS Pathology IN714.0
Role: Laboratory Instructor
Students: Second Year Medical Students
Time: Three-week course in the Fall; 2-3 days per week; one hour preparation and 2 hours teaching per session

e. Advisory and supervisory responsibilities

2000 Supervised and mentored a 2nd year medical student in the laboratory, 500 hr/summer
2001-2002 Supervised and mentored a Harvard undergraduate for senior thesis project, 3-5 days/week for one year
2000- Junior Attending, Autopsy Service, Brigham & Women's Hospital, 150 hr/yr

E. Report of Clinical Activities

1. Department of Pathology, Brigham and Women's Hospital, Autopsy Service

Part III: Bibliography

Original Articles:

1. Drapkin R, Reardon JT, Ansari A, Huang J-C, Zawel L, Ahn K, Sancar A, Reinberg D. Dual role of TFIIH in DNA excision repair and transcription by RNA polymerase II. Nature 1994; 368: 769-772.

2. Shiekhattar R, Mermelstein F, Fisher RP, Drapkin R, Dynlacht B, Wessling HC, Morgan DO, Reinberg D. Cdk-activating kinase complex is a component of human transcription factor IIH. Nature 1995; 374: 283-287.

3. Tong X, Drapkin R, Reinberg D, Kieff E. The 62- and 80-kda subunits of transcription factor TFIIH mediate the interaction with Epstein-Barr virus nuclear protein 2. Proc Natl Acad Sci 1995; 92: 3259-3263.

4. Tong X, Drapkin R, Yalamanchili R, Mosialos G, Kieff E. The Epstein-Barr virus nuclear antigen protein 2 acidic domain interacts with a novel cellular coactivator that can associate with TFIIE. Mol Cell Biol 1995; 15: 4735-4744.

5. Maldonado E, Shiekhattar R, Sheldon M, Cho H, Drapkin R, Rickert P, Lee E, Anderson CW, Linn S, Reinberg D. A human RNA polymerase II complex associated with SRBs and DNA repair proteins. Nature 1996; 381: 86-89.

6. Drapkin R, Le Roy G, Cho H, Akoulitchev S, Reinberg D. Human Cdk-activating kinase (CAK) exists in three distinct complexes. Proc Natl Acad Sci 1996; 93: 6488-6493.

7. Selby CP, Drapkin R, Reinberg D, Sancar A. RNA polymerase II stalled at a thymine dimer: footprint and effect on excision repair. Nucleic Acid Res 1997; 25: 787-793.

8. Le Roy G, Drapkin R, Weis L, Reinberg D. Immunoaffinity purification of the human multisubunit transcription factor IIH. J Biol Chem 1998; 273: 7134-7140.

9. Cantor SB, Bell DW, Ganesan S, Kass E, Drapkin R, Grossman S, Wahrer DCR, Sgroi DC, Lan WS, Haber DA, Livingston DM. BACH1, a novel helicase-like protein, interacts directly with BRCA1 and contributes to its DNA repair function. Cell 2001; 105: 149-160.

10. Fuchs M, Gerber J, Drapkin R, Sif S, Ikura T, Ogryzko V, Lane WS, Nakatani Y, Livingston DM. The p400 complex is an essential E1A transformation target. Cell 2001; 106: 297-307.

11. Ganesan S, Silver DP, Greenberg RA, Avni D, Drapkin R, Miron A, Mok SC, Randrianarison V, Brodie S, Salstrom J, Rasmussen TP, Klimek A, Marrese C, Marahrens Y, Deng C-X, Feunteun J, Livingston DM. BRCA1 supports XIST RNA concentration on the inactive X chromosome. Cell 2002, 111: 393-405.

12. Groisman R, Polanowska J, Kuraoka I, Sawada J, Saijo M, Drapkin R, Kisselev AF, Tanaka K, Nakatani Y. The ubiquitin ligase activity in the DDB2 and CSA complexes is differentially regulated by the COP9 signalosome in response to DNA damage. Cell 2003; 113: 357-367.

13. Drapkin RI, Genest DR, Holmes LB, Huang T, Vargas SO. Unilateral transverse arm defect with subterminal digital nubbins. Pediatr Dev Pathol. 2003; 6:348-54.

14. Ganesan S, Silver DP, Drapkin R, Greenberg R, Feunteun J, Livingston DM. Association of BRCA1 with the inactive X chromosome and XIST RNA. Phil Trans R Soc Lond B 2004; 359: 123-128.

15. Cantor S*, Drapkin R*, Zhang F, Lin Y, Han J, Pamidi S, Livingston DM. The BRCA1-associated protein BACH1 is a DNA helicase targeted by clinically relevant inactivating mutations. Proc Natl Acad Sci 2004; 101: 2357-2362. * *denoted equal contribution.*

16. Drapkin R, Crum CP, Hecht J. Expression of candidate tumor markers in ovarian carcinoma and benign ovary: evidence for a link between epithelial phenotype and neoplasia. *Submitted to Human Pathology.*

Reviews, Chapters, and Editorials:

1. Drapkin R, Merino A, Reinberg D. Regulation of RNA polymerase II transcription. Curr Op Cell Biol 1993; 5: 469-476.

2. Drapkin R, Reinberg D. The multifunctional TFIIH complex and transcriptional control. Trends Biochem Sci 1994; 19: 504-508.

3. Drapkin R, Reinberg D. The essential twist. Nature 1994; 369: 523-524.

4. Drapkin R, Sancar A, Reinberg. Where transcription meets repair. Cell 1994; 77: 9-12.

5. Maldonado E, Drapkin R, Reinberg D. Purification of human RNA polymerase II and general transcription factors. In Adhya S, editor. Methods in Enzymology. San Diego: Academic Press Inc.; 1996. p 72-100.

6. Olave I, Drapkin R, Reinberg D. Transcription and Transcriptional Control: an overview. In Morris D, Harford J, editors. Metabolism and post-transcriptional gene regulation. New York: Wiley-Liss Inc; 1997. p. 23-42.

7. Reinberg D, Orphanides G, Ebright R, Akouitchev S, Carcamo J, Cho H, Cortes P, Drapkin R, Flores O, Ha I, Inostroza J, Kim S, Kim T-K, Kumar P, Lagrange T, Le Roy G, Lu H, Ma D-M, Maldonado E, Merino A, Mermelstein F, Olave I, Shiekhattar R, Stone N, Sun X, Weis L, Yeung K, Zawel L. The RNA polymerase II- general transcription facotrs: past, present, and future. In Cold Spring Harbor Symposia on Quantitative Biology 1998; 53: 83-103.

8. Drapkin R, Reinberg D. RNA synthesis in Encyclopedia of Life Sciences, http://www.els.net, London: Nature Publishing Group, 2002.

9. Drapkin R, Hecht J. The Origins of Ovarian Cancer: Hurdles and Progress. The Women's Oncology Review 2002; 2: 261-268.

Thesis:

Drapkin RI. Studies on the DNA nucleotide excision repair and cell cycle properties of transcription initiation factor TFIIH [dissertation]. Piscataway (NJ): University of Medicine and Dentistry of New Jersey; 1996.

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EDUCATION:

1996 M.D. University of Zagreb School of Medicine, Zagreb, Croatia
1990 High school for Mathematics and Computer Sciences (MIOC), Zagreb, Croatia

LICENSURE:

1998 Medical License
(Issued by the Croatian National Medical Licensing Board)

HONORS AND AWARDS:

2003 *Dana Farber/ Harvard Cancer Center Ovarian Cancer Research Program Fellowship Award;*
Project title: PI3K/Akt and Ras/MAPK signaling in three-dimensional ovarian cancer model system
1996 *Zagreb University Rector's Award* for the best original student research project in 1995/96
Title: Hypertext as a Tool for Creation of Multimedia Databases in Biomedical Sciences
1989 Winner of the Republic Competition of Young Scientists (Biology), Zagreb, Croatia
1989 Gold medal at National Competition of Young Scientists (Biology), Skopje, Yugoslavia

PROFESSIONAL EXPERIENCE:

Research experience

Postdoctoral fellow

2003 – present **Harvard Medical School**, Boston, MA
Department of Cell Biology (John Blenis, Ph.D.)
Project: PI3K/Akt and Ras/MAPK signaling in three-dimensional ovarian cancer model system

1998 – 03 **Stanford University School of Medicine**, Stanford, CA
Division of Oncology (Branimir I. Sikic, M.D.)
Projects: Genetic variations in β-tubulin as determinants of clinical response to taxanes.
Influence of extracellular matrix and growth factor stimulation on kinetics of paclitaxel-induced apoptosis.
C/EBP-mediated transcriptional regulation of *MDR1* gene expression.
Microarray gene expression profiling of germ cell tumors.

1998 **Karl Franzens University**, Graz, Austria
Institute of Pathology (Gerald Hoefler, M.D.)
Projects: Establishment of primary cell cultures from mouse and human colon cancers in reconstituted basement membrane gel (Matrigel®). Expression profiles of growth factor receptors in primary colon cancers and derived cell lines.

Graduate research

1995 – 97 **Institute "Rudjer Boskovic"**, Zagreb, Croatia
Division of Molecular Medicine (Kresimir Pavelic, M.D., Ph.D.)
Project: Expression and role of growth factor receptors, oncogenes and tumor-suppressor genes in human malignancies.

1992 - 95 **Zagreb University School of Medicine**, Zagreb, Croatia
Department of Chemistry and Biochemistry (Ivan Kracun, M.D., Ph.D.)
Project: Distribution and biochemical properties of gangliosides in central nervous system and neuroblastoma cell lines.
Department of Anatomy (Ivica Kostovic, M.D., Ph.D.)
Training in neuropathohistology.

Undergraduate research

1988 – 90 **Institute "Rudjer Boskovic"**, Zagreb, Croatia
Laboratory for Electron Microscopy (Mercedes Wrischer, Ph.D.)
Project: Influence of herbicides on photosynthetic activity in wheat leaf.

1989 **Pliva Research Institute**, Zagreb, Croatia
Laboratory for Molecular Genetics (Zeljko Kucan, Ph.D.)
Honors Summer School. Seminars and lab courses in molecular biology.

Teaching experience

2000 - 03 Stanford University School of Medicine, Division of Oncology, Stanford, CA
Supervised and advised two undergraduate students.

1996 *Teaching Assistant*, Department of Computer Sciences, School of Medicine, Zagreb, Croatia
Initiated and created several official web pages (including those for the Department of Molecular Medicine, Institute "Rudjer Boskovic" and Zagreb University School of Medicine)

1994 - 95 *Teaching Assistant*, Department of Chemistry and Biochemistry, School of Medicine, Zagreb, Croatia. Supervised and advised graduate students. Assisted in Biochemistry lab courses.

Consulting experience

2001 *Celera Genomics*, South San Francisco, CA
Curation of proteins for Celera's proprietary Panther™ Protein Classification, web-based software designed to predict novel proteins and establish phylogenetic context with other proteins.

1999 *American Institute for Biological Sciences (AIBS)*, Washington DC
Breast Cancer Research Program Knowledge Harvesting Project.

Clinical experience

1997 Medical Internship in Zagreb University Hospital, Zagreb, Croatia

MEMBERSHIPS:

American Association for Cancer Research
Croatian Biochemical Society

LANGUAGES:

English, Croatian, German

PUBLICATIONS, INVITED LECTURES, PRESENTATIONS:

Publications

1. **Sale, S.**, Sung, R., Shen, P., Yu, K., Wang, Y., Duran, G.E., Kim, Y.K., Fojo, T., Oefner, P.J., and Sikic, B.I. Conservation of the Class I ß-*Tubulin* Gene in Human Populations and Lack of Mutations in Lung Cancers and Paclitaxel-resistant Ovarian Cancers. Molecular Cancer Therapeutics. 1: 215-225, 2002.
2. **Sale, S.**, Oefner, P., Sikic, B.I. Re: Genetic analysis of the β-tubulin gene, *TUBB* (Class I or M40), in non- small-cell lung cancer. Journal of the National Cancer Institute. 94: 776-777, 2002.
3. Chen GK, **Sale S**, Tan T, Ermoian RP, and Sikic BI. C/EBP (NF-IL6) transactivates the human MDR1 gene by interaction with an inverted CCAAT box in human cancer cells. Molecular Pharmacology, 2004, In press.
4. **Sale, S.**, Lacayo, N., Stuber, C., Wang, Y., Sikic, B.I. Distinct gene expression profiles of cured and non-cured germ cell tumors. In preparation.

Invited Lectures

1. Dubrovnik Summer School in Methods in Molecular Medicine, Zagreb, Croatia, September 1997. Title: "Principles and Practice of Image Analysis in Molecular Biology."
2. Mayo Clinic, Rochester, Minnesota, May 2002. Title: "β-tubulin and Resistance to Taxanes - Perfect Target, Wrong Weapon ?"

Presentations

1. **Sale, S.**, Bernic, L, Anusic, M. Differential distribution of protein kinase C in the human brain, and its decrease during ageing, is related to the alteration of gangliosides.9th International Medical Students Conference, Istanbul, Turkey, 1993. Oral presentation.
2. **Sale, S.**: Gangliosides in SH-SY5Y neuroblastoma cell line. EISS - EMSA International Scientific Symposium, Prague, Czechoslovakia, 1994. Oral presentation.
3. **Sale, S.**: Decrease of GM3-ganglioside concentration in human SH-SY5Y neuroblastoma cell line under retinoic acid treatment. EISS - EMSA International Scientific Symposium, Prague, Czechoslovakia, 1994. Oral presentation.
4. **Sale, S.**, Συνγ, P.,Ωανγ, Ψ., Δυραν, Γ.Ε., Οεφνερ, Π.θ., ανδ Σικιχ, B.I. β -1 Tubulin Polymorphisms and Responsiveness to Paclitaxel Therapy in Ovarian Carcinoma. AACR Annual Meeting, New Orleans, March 2001. Poster.
5. **Sale, S.**, Sung, R., Shen, P.,Yu, K., Wang, Y., Duran, G.E., Kim, Y.K., Fojo, T., Oefner, P.J., and Sikic, B.I. Conservation of the Class I ß-*Tubulin* Gene in Human Populations and Lack of Mutations in Lung Cancers and Paclitaxel-resistant Ovarian Cancers. AACR Annual Meeting, San Francisco, April 2002. Poster.
6. **Sale, S.**, Hromas, R., Juric, D., Francisco, B., Yu, R., Lacayo, N., Stuber, C., Wang, Y., Tibshirani, R., and Sikic, B.I. Distinct gene expression profiles of cured and non-cured germ cell tumors. AACR Annual Meeting, Washington DC, June 2003. Poster.

CURRICULUM VITAE

Part I: General Information

Name:	Yong Zhan
Date of Birth:	November 13, 1971
Place of Birth:	Liaoyang, P. R. China
Citizenship:	P.R.China
Marital Status:	Married to Lei Yuan; one daughter Michelle Z. Zhan
Home Address:	1600 Beacon Street, #1007 Brookline, MA 02446 U.S.A.
Lab Address:	Pediatric Surgical Research Laboratories 55 Fruit St., Warren 1024 Massachusetts General Hospital Boston, MA 02114 U. S. A.
Work Phone #:	617-726-1746
Home Phone #:	617-739-1424
E-Mail:	yzhan@partners.org

Education:

1989-1996 M.D. China Medical University, Shenyang, P.R. China

Academic Positions:

1995-1996	Research Assistant in Cancer Research Institute, China Medical University
1996-1998	Assistant, Department of Surgery of First Teaching Hospital/Research Associate in Cancer Research Institute, China Medical University
1998-2000	Instructor, Department of Surgery of First Teaching Hospital, Cancer Research Institute, China Medical University
2000-2002	Research Associate in Program in Molecular Medicine, University of Massachusetts Medical School
2002-	Research Fellow in Pediatric Surgical Research Laboratories, Massachusetts General Hospital, Harvard Medical School

Professional Societies:

American Society of Biochemistry and Molecular Biology (ASBMB)
China Medical Association (1996~2000)

Awards and Funding:

Fellowship, Ovarian Cancer Research Training Program of DFCI/HCC (2003-)
Excellent Young Investigators, China Medical University (1999)

China Medical University Fellowship (1990-1994)
Best Students of the Year, China Medical University (1990)

Part II, Research and Teaching Experience

Jun, 2002 – present: Research Fellow, Pediatric Surgical Research Laboratories, Mass. General Hospital, Harvard Medical School. Advisor: Patricia K. Donahoe, M.D.

Research Project: Mullerian inhibiting substance signaling

1. Identify the downstream signal transduction effectors of MIS during Mullerian duct regression
2. Mullerian inhibiting substance(MIS) signaling and the anticancer effect

Oct, 2000 – Jun, 2002: Research Associate, Program in Molecular Medicine, University of Massachusetts Medical School. Advisor: G. Wayne Zhou, Ph.D.

Research Projects: The Phox Homology (PX) domain-dependent, phosphoinositide-mediated protein membrane localization

1. The role of phosphoinositides in activation of phox homology (PX) domain- containing proteins
2. Structural study of phosphoinositide-interacting PX domains

Jul, 1996 – Sept, 2000: Research associate, Instructor, Cancer Research Institute, China Medical University.

Research Projects: Molecular carcinogenesis of pancreatic (exocrine and endocrine) tumors

1. The alteration of p16 gene and its mRNA transcription during pancreactic carcinogenesis
2. Cell composition study of pancreatic tumors: origination of pancreatic tumors from the pluripotent cell

Part III. Conference Presentation

Zhan Y, He D, Virbasius JV, Song X, Pomerleau DP, Zhou GW. The $p40^{phox}$ and $p47^{phox}$ PX domains of NADPH oxidase target cell membranes via direct and indirect recruitment by phosphoinositides.
'2003 American Society of Biochemistry and Molecular Biology (ASBMB) Annual Meeting (San Diego, CA, U.S.A)

Zhan Y, He D, Virbasius JV, Song X, Pomerleau DP, Zhou GW. The $p40^{phox}$ and $p47^{phox}$ PX domains of NADPH oxidase translocate to cell membranes via direct and indirect recruitment by phosphoinositides.
'2003 17th Symposium of the Protein Society Meeting (Boston, MA, U.S.A)

Song X, Zhang A, Liang X, **Zhan Y**, Virbasius JV, Czech MP, Zhou GW. Phox homology domains specifically bind phosphoinositol phosphates.
Scientific Conference of UMass Annual Retreat. Oct, 2001, Woodshole, MA.

Li J, **Zhan Y**, Zhou JP. Origination of pancreatic endocrine tumors from the pluripotent cell: Multiple cell constituents present in pancreatic endocrine tumors
'1999 China Experimental Surgery and Surgical Oncology Meeting (Wuhan, China)

Zhan Y, Li J. Different expression of endocrine marker in functional and non-functioning pancreatic endocrine tumors
'1997 China Surgical and Surgical Oncology Society (Northeast Division) Conference (Shenyang, China)

Part IV. Publications

Original Articles—

1. **Zhan Y**, Virbasius JV, Song X, Pomerleau DP, Zhou GW. The $p40^{phox}$ and $p47^{phox}$ PX domains of NADPH oxidase target cell membranes via direct and indirect recruitment by phosphoinositides. J Biol Chem 2002,277:4512-4518.

2. Virbasius JV, Song X, Pomerleau DP, **Zhan Y**, Zhou GW, Czech MP. Activation of the Akt-related cytokine-independent survival kinase requires interaction of its phox domain with endosomal phosphatidlinositol 3-phosphate. Proc Natl Acad Sci U S A 2001,98:12908-13.

3. **Zhan Y**, He D, Newberger PE, Zhou GW. The $p47^{phox}$ PX domain of NADPH oxidase targets cell membrane via moesin-mediated association with the actin cytoskeleton. J Cell Biochem. 2004, (in press).

4. Hoshiya M, Christian BP, Cromie WJ, Kim H, **Zhan Y**, MacLaughlin DT, Donahoe PK. Persistent mullerian duct syndrome caused by both a 27 base-pair deletion and a novel splice mutation in the MIS type II receptor gene. Birth Defects Res Part A Clin Mol Teratol. 2003, 67: 868-874.

5.**Zhan Y**, Li J, Ge C, Qu H, He A, Tian Y. Expression of endocrine cells in small intestinal tumors. Chin J Digestion 2000, 20: 92-4.

6.**Zhan Y**, Zhou J, Li J, Guo K, Tong Y, Zheng X, Tian Y, Guo R. Existence of non-endocrine cells in pancreatic endocrine tumors. Chin J Exp Surg 2000,17:112-3.

7. Zhou J, Liu H, **Zhan Y**, Li J. Expression of p16 mRNA in pancreatic cancer. J China Med Univ 2000, 49: 702-3.

8.Zhou J, **Zhan Y**, Li J. Mutation of p16 gene in pancreatic cancers. Chin J Exp Surg 2000,17:185.

9.**Zhan Y**, Li J, Guo R, Tian Y. Detection of serum endothelin levels in paraoperative obstructive-jaundice patients and its clinical significance. Chin J General Surg 1999,14:348-9.

10.**Zhan Y**, Li J, Qu H, Ge C, Tian Y. Immunohistochemical study of VIPoma. Journal of Surgery (Concepts & Practice) 1999, 4:239-40.
11.Li J, **Zhan Y**, Qu H, Zheng X, Tian Y, Shen K. Cell constituents of pancreatic endocrine tumors and their origin. Chin J Digestion 1998, 18:21-3.
12.Zheng X, Guo K, Tian Y, Li J, Guo R, **Zhan Y**, Song M, Shen K. Cellular composition and anatomic distribution in nonfunctioning pancreatic endocrine tumors: immunohistochemical study of 30 cases. Chin Med J (Engl) 1998, 111:373-6.
13.**Zhan Y**, Li J, Qu H, Zheng X, Tian Y. Expression of NSE, CgA, and Syn in pancreatic endocrine tumors. J China Med Univ 1998, 47: 691-2.

Review—

Zhan Y, Song X, Zhou GW. Structural analysis of regulatory protein domains using GST-fusion proteins. Gene 2001, 281:1-9.

FF Principal Investigator/Program Director *(Last, first, middle)*: Blenis, John

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
John Blenis	Professor of Cell Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of California, Berkeley, CA	B.A.	1973-1977	Biochemistry
Michigan State University, E. Lansing, MI	Ph.D.	1978-1983	Biochemistry
Harvard University, Cambridge, MA	Post-doc	1983-1987	Cell/Mol. Biology

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Professional Experience

1987-1989 Assistant Professor, Dept. of Molecular Biology, Northwestern University Med. School, Chicago
1989-1992 Assistant Professor, Department of Cellular and Molecular Physiology, Harvard Medical School
1992-1995 Associate Professor, Department Cell Biology, Harvard Medical School
1996- Professor, Department of Cell Biology, Harvard Medical School

Honors, Awards and Grants

1973-1977 California State Scholarship and Loan Commission Scholarship.
1983-1984 Damon Runyon-Walter Winchell Cancer Fund Fellowship.
1984-1987 NIH Postdoctoral Fellowship.
1988-1989 Leukemia Research Foundation, Inc. fellowship
1990-1992 American Cancer Society - Junior Faculty Research Award.
1993-1998 American Heart Association Established Investigator Award
1995, 1997 Vice Chair & Chair, Mol. & Genetic Basis of Cell Proliferation, Gordon Research Conference
1998-2000 Hoechst Marion Roussel Exploratory Award, "Signal Transduction During Apoptosis."
2000 Keynote Address, Toronto Signal Transduction Symposium
1988-2013 NIH/NCI Grant (MERIT award) "Mitogenic and Oncogenic Regulation of ERK/RSK Signaling"
1995-2008 NIH/GM Grant, "Signal Transduction to pp70S6k."

Publications (partial listing of 108)

28. Wood K, Sarnecki C, Roberts TM and Blenis J. c-Ras mediates nerve growth factor receptor modulation of three signal-transducing protein kinases: MAP kinase, Raf-1 and RSK. Cell 1992; 68:1041-1050.
29. Chung J, Kuo C, Crabtree GR and Blenis J. Rapamycin: FKBP specifically blocks growth-dependent activation of and signaling by the 70kD-S6 protein kinases. Cell 1992; 69:1227-1236.
30. Kuo CJ, Chung J, Fiorentino DF, Flanagan WM, Blenis J and Crabtree GR. Rapamycin specifically inhibits IL-2-induced activation of p70-S6 kinase. Nature 1992; 358:70-73.
36. Chen R-H and Blenis J. Phosphorylation of the c-Fos transrepression domain by MAP kinase and RSK. Proc. Natl. Acad. Sci. USA 1993; 90: 10952-10956.
43. Chung J, Grammer T, Lemon K, Kazlauskas A, and Blenis J. PDGF- and insulin-dependent pp70S6k activation mediated by phosphatidylinositol-3-OH kinase. Nature 1994; 370: 71-75.
46. Monfar M, Lemon KP, Grammer T, Lemon K, Cheatham L, Vlahos CJ and Blenis J. Activation of pp70/85-S6 kinases in IL-2-responsive lymphoid cells is mediated by phosphatidylinositol 3-kinase and inhibited by cyclic adenosine-3',5'-monophosphate. Mol. Cell. Biol. 1995; 15: 326-337.
51. Cheatham L, Monfar M, Chou MM and Blenis J. Structural and functional analysis of p70 S6 kinase. Proc. Natl. Acad. Sci. USA, 1995; 92: 11696-11700.

53. Fisher T L and Blenis J. Evidence for two catalytically active kinase domains in pp90rsk. Mol. Cell. Biol., 1996; 16: 1212-1219.
54. Chen R-H, Juo P, Curran T and Blenis J. MAP kinase and RSK facilitate transformation induced by c-Fos. Oncogene, 1996; 12: 1493-1502.
57. Chou MM and Blenis J. The 70kD S6 kinase complexes with and is activated by the Rho family G proteins Cdc42 and Rac1. Cell, 1996; 85: 573-583.
64. Juo P, Kuo CJ, Reynolds SE, Konz RF, Raengeaud J, Davis RJ, Biemann H-B and Blenis J. Fas activation of the p38 MAPK signaling pathway requires ICE/CED-3 family proteases. Mol. Cell. Biol. 1997; 17: 24-35.
66. Grammer TC and Blenis J. Evidence for MEK-independent pathways regulating the prolonged activation of the ERK-MAP kinases. Oncogene 1997; 14: 1635-1642.
67. Chung J, Uchida E, Grammer TC and Blenis J. STAT3 serine phosphorylation by ERK-dependent and -independent pathways negatively modulates its tyrosine phosphorylation. Mol. Cell. Biol.1997;17:6508- 6516.
69. Juo P, Kuo CJ, Yuan J and Blenis J. Essential requirement for caspase-8/FLICE in the initiation of the Fas-induced apoptotic cascade. Curr. Biol. 1998; 8: 1001-1008.
72. Romanelli A, Martin KA, Toker A and Blenis J. P70 S6 kinase is regulated by atypical protein kinase Cζ and participates in a PI3-K-regulated signaling complex. Mol. Cell. Biol. 1999; 19: 2921-2928.
73. Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, Anderson MJ, Arden KC, Blenis J and Greenberg ME. Akt promotes cell survival by phosphorylating and inhibiting a forkhead transcription factor. Cell 1999; 96: 857-868.
75. Lee-Fruman KK, Kuo CJ, Lippincott J, Terada N and Blenis J. Characterization of S6K2, a novel kinase homologous to S6K1. Oncogene 1999; 18: 5108-5114.
76. Richards SA, Fu J, Romanelli A, Shimamura A and Blenis J. Ribosomal S6 kinase 1 (RSK1) activation requires signals dependent on and independent of the MAP kinase ERK. Current Biology 1999; 9: 810-820
78. Shimamura A, Ballif BA, Richards SA and Blenis J. RSK1 mediates a MEK/MAP kinase cell suvival signal. Current Biology 2000; 10: 127-135.
84. Martin KA, Schalm SS, Romanelli A, Keon KL and Blenis J. S6K2 inhibition by a potent C-terminal repressor domain is relieved by MEK-regulated phosphorylation. J Biol Chem. 2001; 276: 7892-7898.
85. Ballif BA, Shimamura A, Pae E and Blenis J. Disruption of 3-Phosphoinositide-Dependent Kinase 1 (PDK1) Signaling by the anti-tumorigenic and anti-proliferative agent N-α-tosyl-L-phenylalanyl chloromethyl ketone. J Biol Chem. 2001; 276: 12466-12475.
90. Richards SA, Dreisbach VC, Murphy LO and Blenis J. Characterization of regulatory events associated with membrane targeting of p90 ribosomal S6 kinase 1. Mol. Cell. Biol. 2001; 21: 7470-7480.
92. Schalm S and Blenis J. Identification of a conserved motif required for mTOR signaling. Current Biol. 2002; 12: 632-639.
93. Fingar DC, Salama S, Tsou C, Harlow E, Blenis J. Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E. Genes Dev. 2002;16:1472-1487.
95. Manning BD, Tee AR, Logsdon MN, Blenis J and Cantley LC. Identification of the TSC-2 tumor suppressor gene product tuberin as a target of the PI3 kinase/Akt pathway. Mol. Cell 2002; 10: 151-162.
96. Murphy LO, Smith S, Chen R-H, Fingar DC and Blenis J. Molecular interpretation of ERK signal duration by immediate early gene products. Nat. Cell Biol. 2002; 4: 556-564.
97. Tee AR, Fingar DC, Manning BD, Kwiatkowski DJ, Cantley LC and Blenis J. Tuberous Sclerosis Complex-1 and –2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling. Proc. Natl. Acad. Sci. USA 2002; 99: 13571-13576.
98. Romanelli A, Dreisbach V and Blenis J. Characterization of phosphatidylinositol 3-kinase-dependent phosphorylation of the hydrophobic motif site Thr389 in p70 S6 kinase 1. J Biol Chem. 2002;277:40281-40289.
99. Schalm S, Fingar DC, Sabatini DM and Blenis J. TOS motif-mediated raptor binding regulates 4E-BP1 multi-site phosphorylation and function. Current Biology 2003; 13: 797-806.
100. Roux PP, Richards SA and Blenis J. Phosphorylation of p90 ribosomal S6 kinase (RSK) regulates ERK docking and RSK activity. Mol. Cell. Biol. 2003; 23: 4796-4804.
101. Tee AR, Manning BD, Roux P, Cantley LC and Blenis J. The Tuberous Sclerosis Complex gene products, tuberin and hamartin, control mTOR signaling by acting as a GTPase-activating protein complex towards Rheb. Current Biology, 2003; 13: 1259-1268.

102. Tee AR, Anjum R and Blenis J. Inactivation of the tuberous sclerosis complex-1 and –2 gene products occurs by phosphoinositide 3-kinase/Akt-dependent and –independent phosphorylation of tuberin. J. Biol. Chem. 2003; 278:37288-37296.
103. Fingar D, Richardson C, Tee A, Cheatham L, Tsou C and Blenis J. mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4EBP1/eIF4E. Mol. Cell Biol. 2004. 24: 200-216.
104. Murphy LO, MacKeigan JP and Blenis J. A network of immediate early gene products propagates subtle differences in MAP kinase signal amplitude and duration. Mol. Cell Biol. 2004. 24: 144-153.
108. Woo MS, Ohta Y, Rabinovitz I, Stossel TP and Blenis J. Ribosomal S6 Kinase (RSK) regulates phosphorylation of Filamin A on an important regulatory site. Mol. Cell Biol. 2004; 24: 3025-3035.

Principal Investigator/Program Director *(Last, first, middle):* Donahoe, Patricia, K.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Patricia K. Donahoe	Chief, Pediatric Surgical Services, Director Pediatric Surgical Research Laboratories

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Boston University, Boston MA	BS	1958	
Columbia University, New York NY	MD	1964	Medicine
Harvard University, Cambridge MA	MA (Hon)	1989	

NOTE: The Biographical Sketch may not exceed four pages. Items A and B may not exceed two of the four-page limit.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee

1964-69 Surgical Interns, Junior Assistant, Senior & Chief Surgical Resident & Teaching Fellow, Tufts NEMC, Boston
1964-70 Research Fellow in Surgery at Children's Hospital Medical Center, Boston, MA (Dr. Judah Folkman)
1970-71 Clinical and Research Fellow in Surgery, Massachusetts General Hospital, Boston, MA (Dr. Hardy Hendren)
1971-72 Senior Registrar, Alder Hey Children's Hospital and Neonatal Surgical Unit, Liverpool, England
1973- Clinical Associate in Surgery, Assistant in Surgery, Instructor in Surgery, Assistant Surgeon, Associate Visiting Surgeon, and Visiting Surgeon, Massachusetts General Hospital
1973 - Director, Pediatric Surgical Research Laboratory, Massachusetts General Hospital, Boston, MA
1977-79 Assistant Professor of Surgery, (1980-86) Associate Professor of Surgery, (1986) Professor of Surgery, Harvard Medical School (tenured), Boston MA (Marshall K. Bartlett Professor, 1992)
1984 Division of Pediatric Surgery, Massachusetts General Hospital, Boston, MA
1991-03 Chief Pediatric Surgical Services, Massachusetts General Hospital, Boston, MA
1993- Associate Faculty Member, Graduate Program, Biological & Biomedical Sciences, Dept. of Cell Biology, HMS, Boston, MA
2003 Chief of Pediatric Surgical Services, Emeritus, Massachusetts General Hospital, Boston, MA

Awards and other Professional Activities:

1980- Member, Committee on Research, Massachusetts General Hospital
1980-82 Chairman, Subcommittee on the Review of Research Proposals, Committee on Research, MGH
1982-88 Visiting Committee, Whitaker College, MIT
1985 Vice Chairman, Chairman and Member, Executive Committee on Research, Massachusetts General Hospital.
1987 Fellow, American Academy of Arts & Sciences
1988 General Executive Committee/Chiefs' Council, Massachusetts General Hospital, Boston, MA
1990-93 Governor, American Pediatric Surgical Association
1991- Fellow, Institute of Medicine, National Academy of Sciences
1992 Chairman, Gordon Conference, Reproductive Tract Biology
1993-97 Scientific Advisory Board, Memorial Sloan-Kettering Cancer Center
1993-96 Scientific Advisory Board, Wyeth-Ayerst
1997-01 National Advisory Council, NICHD
1998 Member and Chairman, Scientific Advisory Board - St. Jude's Medical Center
1998-99 1st Vice President, American Surgical Association
1999- Fellow, American Association for the Advancement of Science
1999- Fellow, National Academy of Science
2001 President, Boston Surgical Society
2004 Fred Conrad Koch Award, The Endocrine Society
2004 Honorary Doctor of Science, Northwestern University

B. Selected peer-reviewed publications (in chronological order). Do not include publications submitted or in preparation. (Representation) Total number: 210

1. Catlin EA, Ezzell R, Donahoe PK, Manganaro T, Ebb RG, MacLaughlin DT. Müllerian Inhibiting Substance Binding and Uptake. Developmental Dynamics, (formerly Am J Anat.), 1992; 193(4):295-299.
2. MacLaughlin DT, Hudson PL, Graciano AL, Kenneally MK, Ragin RC, Manganaro TF, Donahoe PK. Mullerian duct regression and anti-proliferative bioactivities of MIS resides in its carboxy-terminal domain. Endocrinol 1992; 131(1):291-6.
3. MacLaughlin DT, Levin RK, Catlin EA, Taylor LA, Preffer FI, Donahoe PK. Identification of Müllerian Inhibiting Substance Specific Binding in Human Cell Lines. Hormone and Metabolic Research, 1992; 24:570-575.
4. Hirobe S, He WW, Lee MM, Donahoe PK. Müllerian Inhibiting Substance Messenger Ribonucleic Acid Expression in Granulosa and Sertoli Cells Coincides with Their Mitotic Activity. Endocrinology 1992; 131(2):854-62.
5. Donahoe PK. MIS in Reproduction and Cancer. Molecular Reproduction and Development, 1992; 32:168-72.
6. Boveri, JF, Parry RL, Gustafson ML, Lee KW, Donahoe PK. Transfection of the Mullerian Inhibiting Substance gene inhibits local and metastatic tumor growth. Int J Oncology 1993; 2:135-43.
7. Taketo, T, Saeed, J, Manganaro, T, Takahashi, M Donahoe, PK (1993). Mullerian inhibiting substance production associated with loss of oocytes and testicular differentiation in the transplanted mouse XX gonadal primordium.Biol Reprod 49(1):13-23.
8. Haqq CM, King CY, Donahoe PK, Weiss MA. SRY Recognizes conserved DNA Sites in Sex-specific Promoters PNAS 1993; 90:1097-1101.
9. Gustafson ML, Lee MM, Asmundson L, MacLaughlin DT, Donahoe PK. Mullerian Inhibiting Substance in the diagnosis and management of intersex and gonadal abnormalities. J Pedi Surg, 1993; 28:439-44.
10. He WW, Gustafson ML, Hirobe S, Donahoe PK. The Developmental Expression of Four Novel Serine/Threonine Kinases Homologous to the Activin/TGF__ II Receptor Family. Developmental Dynamics 1993; 196:133-42.
11. Catlin EA, Ezzell RM, Donahoe PK, Gustafson ML, Son EV, MacLaughlin DT. Identification of a receptor for human Müllerian Inhibiting Substance. Endocrinology, 1993,133(6):3007-3013.
12. Bassing CH, Yingling J, Howe D, Wang T, He WW, Gustafson M, Shah P, Donahoe PK, Wang XF. Identification of a TGF__ type I receptor that signals to activate gene response by complexing with the type II receptor. Science, 1994; 263:87-89.
13. Wang TW, Donahoe PK, Zervos AS. Specific interaction of type I receptors of the TGF__ family with the immunophilin FKBP12. Science, 1994, 265:674-6.
14. Haqq, CM, King, CY, Ukiyama, E, Falsafi, S, Haqq, TN, Donahoe, PK and Weiss, MA (1994). Molecular basis of mammalian sexual determination: activation of Mullerian inhibiting substance gene expression by SRY. Science 266 (5190):1494-500.
15. Suen HC. Losty P, Donahoe PK, Schnitzer JJ. Combined antenatal thyrotropin-releasing hormone and low-dose glucocorticoid therapy improves the pulmonary biochemical immaturity in congenital diaphragmatic hernia. J Pediatr Surg 1994; 29(2):359-363.
16. Suen HC, Losty PD, Donahoe PK, Schnitzer JJ. Accurate method to study static volume-pressure relationships in small fetal and neonatal animals. J Appl Physiol 1994;77(2):1036-1043.
17. Alles AJ, Losty PD, Donahoe PK, Manganaro TF, Schnitzer JJ. Embryonic cell death patterns associated with nitrofen-induced congenital diaphragmatic hernia. J Pediatr Surg 1995;30(2):420-426.
18. Losty P, Suen HC, Manganaro TF, Donahoe PK, Schnitzer JJ. Prenatal hormonal therapy improves pulmonary compliance in the nitrofen induced CDH rat model. J Pediatr Surg 1995;30(3):420-426.
19. Hedrick HL, Pacheco BA, Losty PD, Donahoe PK, Schnitzer JJ. Dexamethasone increases expression of surfactant associated protein mRNA in rats with nitrofen-induced congenital diaphragmatic hernia. Surgical Forum 1995;XLVI:654-657.
20. Simpson BB, Ryan DP, Doody DP, Schnitzer JJ, Kim SH, Donahoe PK. Type IV laryngotracheoesophageal clefts: Surgical management for long-term survival. J Pediatr Surg 1996;31(8):1128-1133.
21. Schnitzer JJ, Hedrick HL, Pacheco BA, Losty PD, Ryan DP, Doody DP, Donahoe PK. Prenatal glucocorticoid therapy reverses pulmonary immaturity in congenital diaphragmatic hernia in fetal sheep. Ann Surg 1996;224(4):430-439.
22. Wang, TW, Li, BY, Danielson PD, Shah PC, Rockwell S, Lechleider RJ, Martin J, Manganaro T, Donahoe PK. The immunophilin FKBP12 functions as a common inhibitor of the TGF__ family type I receptors. Cell, 86:1-20. 1996.
23. Kurian MS, Sainz de la Cuesta R, Waneck GL, MacLaughlin DT, Manganaro TF, Donahoe PK. Cleavage of Müllerian Inhibiting Substance activates antiproliferative effects *in vivo*. Clinical Cancer Research, 1995; 1:343-9.
24. Peters R, King C-Y, Ukiyama E, Falsafi S, Donahoe PK, Weiss M. An SRY mutation causing human sex reversal resolves a general mechanism of structure-specific DNA recognition: Application to the 4-Way DNA junction. Biochem 1995; 34:4569-76.
25. Wang TW, Danielson PD, Li BU, Shah PC, Kim SD, Donahoe PK. $p21^{ras}$ Farnesyltransferase alpha subunit in TGF-Beta and Activin Signaling. Science, 1996, 271: 1120-2.
26. Teixeira J, He WW, Shah PC, Morikawa N, Lee MM, Catlin EA, Hudson PL, Wing J, MacLaughlin DT, Donahoe PK. Developmental expression of a candidate Müllerian Inhibiting Substance type II receptor. Endocrinology, 1996; 137:160-65.
27. Lee MM, Donahoe PK, Hasegawa T, Silverman B, Crist, GB, Best S, Hasegawa Y, Noto RA, Schoenfeld D, MacLaughlin DT "Müllerian Inhibiting Substance (MIS) in humans: Normal levels from infancy to adulthood, J Clin Endo Met, 1996; 81:571-76.
28. Maggard MA, Catlin EA, Hudson PL, Donahoe PK, MacLaughlin DT. Reduction of Epidermal Growth Factor Receptor Phosphorylation by Activated Mullerian Inhibiting Substance is Vanadate-Sensitive. Metabol 1996; 45:190-5.
29. Pacheco BA, Islam S, Sung P-K, Chang WT, Manganaro TF, Donahoe PK, Schnitzer JJ. Antioxidants reverse fetal rat pulmonary hypoplasia in vitro. Surgical Forum 1997;XLVIII:652-655.
30. Catlin EA, Tonnu V, Ebb R, Pacheco BA, Ezzell R, Donahoe PK, Manganaro TF, Teixeira JM. Müllerian inhibiting substance inhibits branching morphogenesis and induces apoptosis in fetal rat lung, Endocrinology 1997; 138:790-6.
31. Lee MM, Donahoe PK, Silverman BL, Hasegawa T, Hasegawa Y, Gustafson ML, Chang YC, MacLaughlin DT. Müllerian Inhibiting Substance in the evaluation of children with nonpalpable gonads. N Engl J Med 1997; 336:1480-6.
32. Masiakos PT, MacLaughlin DT, Teixeira J, Chen A, Shah PC, Kehas DJ, Fuller AF, Preffer FI, Dombkowski DM, Donahoe PK. Preclinical trial of recombinant human Müllerian inhibiting substance (rhMIS) in the treatment of ovarian cancer. Surgical Forum 1997;48:662-664.
33. Haqq CM, Donahoe PK. Regulation of Sexual Dimorphism in Mammals. Physiological Reviews, 1998; 78(1):1-33.
34. Lane AH, Lee MM, Fuller AF, Kehas DJ, Donahoe PK, MacLaughlin DT. Diagnostic Utility of Mullerian Inhibiting Substance Determination in Patients with Primary and Recurrent Granulosa Cell Tumors. Gynecol. Oncol. 1999 Apr;73(1):51-5.
35. Lee MM, Seah C, Masiakos PT, Sottas C, Preffer F, MacLaughlin DT, Donahoe PK, Hardy M. Mullerian Inhibiting Substance Type II Receptor Expression and Binding in Primary Leydig cells. Endocrinology, Jun;140(6):2819-27.

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49. Ha TU, Segev DL, Barbie D, Masiakos PT, Tran TT, Dombkowski D, Glander M, Clarke T, Lorenzo HK, Donahoe PK, Maheswaran S. Müllerian Inhibiting Substance inhibits cell growth through a Rb independent mechanism. J Biol Chem. 2000 Nov 24;275(47):37101-9.
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51. Stephen AE, Masiakos Pt, Segev DL, Vacanti JP, Donahoe PK and MacLaughlin DT. Tissue-engineered cells producing complex recombinant proteins inhibit ovarian cancer *in vivo*. PNAS 2001 Mar 13; 98:3214-3219.
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59. Segev DL, Hoshiya Y, Tran TT, Stephen AE, MacLaughlin DT, Donahoe PK, and Maheswaran S. Müllerian Inhibiting Substance regulates NFκB signaling in the prostate *in vitro* and *in vivo*. PNAS 2002;99(1): 239-244.
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67. Florea C, Kia H., Krebs C, Schwanzel-Fukuda M., Ogawa S., Donahoe PK, MacLaughlin DT, and Pfaff D. MIS Type II Receptor mRNA Expression in Embryonic Mouse Brain and Anterior Pituitary. J Comp Neurol 2003.
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70. Barbie TU, Barbie DA, MacLaughlin DT, Maheswaran S, and Donahoe PK. Mullerian Inhibiting Substance inhibits cervical cancer cell growth via a pathway involving p130 and p107. PNAS 2003;100(26):15601-15606
71. Houk CP, Pearson EJ, Martinelle N, Donahoe PK, Teixeira J. Feedback Inhibition of Steroidogenic Acute Regulatory Protein Expression *in Vitro* and *In Vivo* by Androgens. Endocrinology 2004; 145(3):1269-1275.
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174.

C. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and responsibilities of principal investigator identified above.

"Müllerian Inhibiting Substance" PI: Donahoe
Agency: National Cancer Institute
Type: R01 CA17393, Years 22-24, Period June 1, 1978 to June 30, 2004
The goal of this grant is to study Müllerian Inhibiting Substance in normal and abnormal tissues and to relate these findings to human ovarian cancer.

"MIS receptors-Novel Serine/Threonine Kinase Components" PI: Donahoe
Agency: National Institute of Child Health and Human Development
Type: R01 HD32112, Years 1-5, Period August 1, 1994 to May 31, 2004
The goal of this grant is to characterize the putative MIS type I receptor (R1) and three other type I receptors (R2-4) by binding experiments in tissue culture and by gene disruption in mice. It also aims to characterize the MIS specific Smads, and target genes for MIS

"Comparative Genomics to Correct Human Lung Hypophasia" Program Project, PI: Donahoe, Project IV PI: Donahoe
Agency: National Institute of health
Type:PO1 HD-99-008, Years 2-3, Period July 5, 2001 to March 31, 2006
Goal: The goal of this grant is to define genetic or molecular abnormalities that lead to pulmonary hypoplasia, particularly that which is associated with congenital diaphragmatic hernia (CDH). It is our ultimate aim to derive therapeutic strategies from these findings that can be used *in utero* to complement the genetic or molecular defects found.

"Recombinant MIS Cancer Therapeutic Produced in Plants" PI: MacLaughlin, Donahoe is an investigator
Agency: National Cancer Institute
Type:R44 CA73365, Years 1-2, Period July 1, 2001 to June 30, 2003
The goals of this project are to produce bioactive, recombinant MIS in tobacco plants. The role of MGH is to do the purification and testing.

"Neuroendocrine and Gonadal Control of Male Reproduction" Program Project, PI: Crowley
Agency: National Institute of Child Health and Human Development
Type: U54 HD28138, Years 10-14, Period April 1, 2000 to March 31, 2005
Dr. Teixeira is the PI and Donahoe, an investigator on Project 3, "Paracrine Control of Steroidogenesis by MIS"

Principal Investigator/Program Director (Last, first, middle): Livingston, David

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	Emil Frei Professor of Genetics and Medicine
David M. Livingston, M.D.	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Harvard University, Cambridge, MA	A.B.	1961	History
Tufts University Sch. of Medicine, Boston,MA	M.D.	1965	

Research and Professional Experience

1965-67 Intern in Medicine/Jr. Resident in Medicine, Peter Bent Brigham Hospital, Boston, MA.
1967-69 Research Associate, Laboratory of Biochemistry, National Cancer Institute, Bethesda, MD
1969-71 Research Fellow in Biological Chemistry, Harvard Medical School, Boston, MA
1971-72 Senior Staff Fellow, National Cancer Institute, Bethesda, MD
1972-73 Senior Investigator, National Cancer Institute, Bethesda, MD
1973-76 Assistant Professor of Medicine, Harvard Medical School, Boston, MA
1973-77 Senior Clinical Associate, Dana-Farber Cancer Institute; Associate in Medicine, BWH, Boston, MA
1976-82 Associate Professor of Medicine, Harvard Medical School; Sr. Associate in Medicine, BWH, Boston,MA
1977-83 Associate Physician, Dana-Farber Cancer Institute, Boston, MA
1982-92 Professor of Medicine, Harvard Medical School; Physician, BWH, Boston, MA
1983-96 Physician, Dana-Farber Cancer Institute, Boston, MA
1989-91 Vice President, Dana-Farber Cancer Institute, Boston, MA
1991-95 Director and Physician-in-Chief, Dana-Farber Cancer Institute, Boston, MA
1992- Emil Frei Professor of Medicine, Harvard Medical School, Boston, MA
1995-00 Chairman, Executive Committee for Research. Dana-Farber Cancer Institute, Boston, MA
1996- Distinguished Consultant in Cancer Medicine, Dana-Farber Cancer Institute, Boston, MA
1997- Professor of Genetics, Harvard Medical School, Boston, MA
1997- Program Director, Charles A. Dana Division of Human Cancer Genetics, Dana-Farber Cancer Institute
1997-99 Chair, Dana-Farber/Harvard Cancer Center Grant Planning Committee
1999- Member, Dana-Farber/Harvard Cancer Center Executive Committee
1999- Deputy Director, Dana-Farber/Harvard Cancer Center

Licensure and Certification

1969 Massachusetts License Registration #31544
1971 American Board of Internal Medicine Certificate #34251

Honors and Awards

1961 A.B., Cum Laude, Harvard University; 1964/65 Alpha Omega Alpha, Tufts Chapter, President; **1965** Alumni Prizes, highest class rank, Tufts University School of Medicine; **1965** M.D. Magna Cum Laude, Tufts Unversity School of Medicine; **1991**Claire W. and Richard P. Morse Research Award, Dana-Farber Cancer Institute; **1990-** Elected to Institute of Medicine, National Academy of Sciences; **1995-** Elected to National Academy of Sciences; **1997-** Association of American Medical College's Award for Distinguished Research in the Biomedical Sciences, Baxter Allegiance Foundation; **1997**, Brinker International Award for Breast Cancer Research; **2001** Lila Gruber Cancer Research Award, American Academy of Dermatology; 2001, elected to American Academy of Arts and Sciences

Advisory Committees

1992-97 Member, Board of Directors, Damon Runyon-Walter Winchell Cancer Research Fund, NY
1992-96 Member, Board of Scientific Counselors, DCBDC, NCI, NIH
1994-95 Ad hoc Advisory Committee to Review the Internal Program of the NCI
1995-99 Chairman, Board of Scientific Advisors, NCI
1997- President, Board of Directors, Cancer Research Fund, NY

1997-98 Member, Advisory Committee to the Director, NCI
1998- Member, Scientific Review Board, Howard Hughes Medical Institute, Chevy Chase, MD

Selected Publications of David M. Livingston, M.D. (of 178 publications).

Scully R, Ganesan S, Vlasakova K, Chen J, Socolovsky M, Livingston DM. Genetic Aanalysis of BRCA1 Function in a defined tumor cell line. Mol Cell 1999; 4:1093-1099.

Kung AL, Rebel VI, Bronson RT, Ch'ng L-E, Sief CA, Livingston DM, Yao T-P. Gene dose-dependent control of hematopoiesis and hematologic tumor suppression by CBP. Genes Develop 2000; 14:272-277.

Wu X, Ranganathan V, Weisman DS, Heine WF, Ciccone DN, O'Neill TB, Crick KE, Pierve KA, Lane WS, Rathbun G, Livingston DM, Weaver DT. ATM phosphorylation of Nijmegen breakage syndrome protein is required in a DNA damage response. Nature 2000; 405; 477-481.

Wu X, Petrini J, Heine W, Weaver DT, Livingston DM, Chen J. Technical Comment: Independence of N/M/R focus formation and the presence of intact BRCA1. Science 2000; 11.

Eid JE, Kung AL, Scully R, Livingston DM. P300 interacts with the nuclear proto-oncoprotein, SYT, as part of the active control of cell adhesion. Cell 2000; 102: 839-848.

Gaubatz S, Lindeman GJ, Ishida S, Jakoi L, Nevins JR, Livingston DM, Rempel RE. E2F4 and E2F5 play an essential role in pocket protein-mediated G1 control. Molecular Cell 2000; 6: 729-735.

Kung AL, Wang S, Klco JM, Kaelin Jr KG, Livingston DM. Suppression of tumor growth through disruption of hypoxia-inducible transcription. Nature Med 2000; 6: 1335-1340.196

Tibbetts RS, Cortez D, Brumbaugh KM, Scully R, Livingston DM, Elledge SJ, Abraham RT. Functional interactions between BRCA1 and the checkpoint kinase ATR during genotoxic stress. Genes Develop; 2000; 14: 2989-3002.

Scully R, Livingston DM. In search of te tumour-suppressor functions of BRCA1 and BRCA2. Progress Article. Nature 2000; 408:429-432.Gaubatz S, Lees JA, Lindeman GJ, Livingston DM. E2F4 is exported from the nucleus in a crml-dependent manner. Mol Cell Biol 2001; 21: 1384-1392.

Cantor SB, Bell DW, Ganesan S, Kass EM, Drapkin R, Grossman S, Wahrer DCR, Sgroi DC, Lane WS, Haber D, Livingston DM. BACH1, a novel helicase-like protein interacts directly with BRCA1 and contributes to its DNA repair function. Cell 2001; 105: 149-160.

Silver D, Livingston DM. Self-excising retroviral vectors encoding the Cre recombinase overcome Cre-mediated cellular toxicity. Mol Cell 2001; 8:233-243.

Fuchs M, Gerber J, Ikura T, Sif S, Drapkin R, Lane WS, Nakatani Y, Livingston DM. The p400 complex is an essential E1A transformation target. Cell 2001; 106: 297-307.

Joukov V, Chen J, Fox EA, Green JB, and Livingston DM. Functional communication between endogenous BRCA1 and its partner, BARD1, during *Xenopus laevis* development. Proc Natl Acad SCi USA 2001; 98:12078-12083.

Freedman SJ, Sun ZYJ, Poy F, Kung AL, Livingston DM, agner G, Eck MJ. Structural basis for recruitment of CBP/p300 by hypoxia-inducible factor-1□. Proc Natl Acad Sci USA 2002; 99:5367-5372.

Yang H, Williams B, Hinds P, Shih S, Jacks T, Bronson R, Livingston DM. Tumor suppression by a severely truncated species of the retinoblastoma protein. Mol Cell Biol 2002; 22:3103-3110

Ogawa H, Ishiguro K, Gaubatz S, Livingston DM, Nakatani P. A complex containing chromatin modifiers that occupies E2F-and Myc-responsive genes in quiescent cells. Science 2002;296:1132-1136

Rebel VI, Kung AL, Tanner EA, Yang H, Bronson RT, Livingston DM. Distinct role for CREB-binding protein and p300 in haematopoietc stem cell self renewal. Proc Natl Acad Sci USA 2002;99:14789-14794.

Ganesan S, Silver DP, Greenberg RA, Avni D, Drapkin R, Miron A, Mok SC, Randrianarison V, Brodie S, Salstrom J, Rasmussen TP, Klimke A, Marrese C, Marahrens Y, Deng C-X, Feunteun J, Livingston DM. BRCA1 Supports XIST RNA Concentration on the Inactive X Chromosome. Cell 2002; 111: 393-405.

Dahme T, Wood J, Livingston DM , Gaubatz S. Two different E2F6 proteins generated by alternative splicin and internal translation initiation. Eur J Biocem 2002; 269:5030-5036

Storre J, Elsasser H-P, Fuchs M, Ullmann D, Livingston DM, Gaubatz S. Homeotic transformations of the axial skeleton that accompany a targeted deletion of E2F6. EMBO Reports 2002; 3:695-700.

Grossman, SR. Deato, ME. Brignone, C, Chan HM. Kung, A. Tagami, H. Nakatani, Y. and Livingston, D.M. A Ubiquitin ligase activity of p300 promotes the polyubiquitination of p53, Science 2003; 300:342-344

Avni, D., Yang, H., Martelli, F., Hofmann, F., ElShamy, W. and Livingston, D. Active localization of the retinoblastoma protein in chromatin and its response to S phase DNA damage. 2003 Mol . Cell Vol 12: 735-746

Cantor S, Drapkin R, Zhang F, Lin Y, Han J, Pamidi S, and Livingston DM. The BRCA1-associated protein BACH1 is a DNA helicase targeted by clinically relevant inactivating mutations. Proc Natl Acad Sci USA 2004;101:2357-2362.

• OC030067 Principal Investigator/Program Director *(Last, first, middle):* Orsulic, Sandra

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format on preceding page for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Sandra Orsulic	Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Zagreb, Zagreb, Croatia	AB	1991	Engineering/Biology
University of North Carolina at Chapel Hill Chapel Hill, NC	PhD	1996	Molecular Biology

A. Positions and Honors:

Professional Experence/Appointments

1996-1998 Humboldt Fellow, Cell Adhesion & Signaling, Max-Planck Institute in Freiburg, Germany
1998-2000 Fogarty Visiting Fellow, Models for Ovarian Cancer, National Institutes of Health, Bethesda, MD
2000-2002 Research Fellow, Models for Ovarian Cancer, Memorial Sloan-Kettering Cancer Center, New York, NY
2002- Assistant Molecular Pathologist, Department of Pathology, Massachusetts General Hospital, Boston, MA
2002- Assistant Professor of Pathology, Harvard Medical School, Boston, MA

Honors/Awards:

1989 The University of Zagreb Fellowship
1989 IAESTE Award for Exchange Studies at The Hebrew University in Jerusalem, Israel
1990 The University of Zagreb Fellowship
1990 IAESTE Award for Exchange Studies at The University of Reykjavik, Iceland
1991 University of North Carolina Fellowship
1996 Max-Planck Institute Fellowship
1997 Alexander von Humboldt Fellowship
1998 Fogarty Fellowship at the National Institutes of Health
1999 Susan G. Komen Fellowship for Cancer Research

B. Selected peer-reviewed publications:

1. Müller WEG, Slor H, Pfeifer K, Hühn P, Bek A, **Orsulic S**, Ushijima H, Schröder HC. Association of AUUUA-binding protein with A+U-rich mRNA during nucleo-cytoplasmic transport. Journal of Molecular Biology 1992;226:721-733.

2. Peifer M, **Orsulic S**, Sweeton D, Wieschaus E. A role for the Drosophila segment polarity gene Armadillo in cell adhesion and cytoskeletal integrity during oogenesis. Development 1993;118:1191-1207.

3. Peifer M, **Orsulic S**, Pai L-M, Loureiro J. A model system for cell adhesion and signal transduction in Drosophila. Development 1993;Supplement:163-176.

4. **Orsulic S**, Peifer M. The method to stain nuclei of Drosophila for confocal microscopy. Biotechniques 1994;16:441-447.

5. **Orsulic S**, Peifer M. An in vivo structure-function study of Armadillo, the β-catenin homolog, reveals both separate and overlapping regions of the protein required for cell adhesion and for Wingless signaling. The Journal of Cell Biology 1996;134:1283-1300.

6. **Orsulic S**, Peifer M. Wingless lands at last. Current Biology 1996;6:1363-1367.

7. Pai L-M, **Orsulic S**, Bejsovec A, Peifer M. Negative regulation of Armadillo, a Wingless effector in Drosophila. Development 1997;124:2255-2266.

8. Cox R, Pai L-M, Miller JR, **Orsulic S**, Stein J, McCormick C, Audeh Y, Wang W, Moon RT, Peifer M. Membrane-tethered Drosophila Armadillo cannot transduce Wingless signal on its own. Development 1999;126:1327-1335.

9. **Orsulic S**, Huber O, Aberle H, Arnold S, Kemler R. E-cadherin binding prevents α-catenin nuclear localization and β-catenin–LEF-1-mediated transactivation. Journal of Cell Science 1999;112:1237-1245.

10. Fisher GH, **Orsulic S**, Holland E, Hively WP, Li Y, Lewis BW, Williams BO, Varmus HE. Development of a flexible and specific gene delivery system for production of murine tumor models. Oncogene 1999;18:5253-5260.

11. **Orsulic S**, Kemler R. Differential regulation of Eph family members by E-cadherin. Journal of Cell Science 2000;113:1793-1802.

12. **Orsulic S**, Li Y, Soslow RA, Vitale-Cross LA, Gutkind SJ, Varmus HE. Induction of ovarian cancer by defined multiple genetic changes in a mouse model system. Cancer Cell 2002;1:53-62.

13. **Orsulic S**. An RCAS-TVA-based approach to designer mouse models. Mammalian Genome 2002;13:543-547.

14. Balkwill F, Bast RC, Berek J, Chenevix-Trench G, Gore M, Hamilton T, Jacobs I, Mills G, Souhami R, Urban N, **Orsulic S**, Smyth J. Current research and treatment for epithelial ovarian cancer. A Position Paper from the Helene Harris Memorial Trust. European Journal of Cancer 2003; 39:1818-27.

15. **Orsulic, S.** Ovarian Cancer. *In:* Holland E.C. (eds). Mouse Models of Cancer, 1st Ed. John Wiley & Sons, New York *(in press)*

Ovarian Cancer Basic Research Seminars
Schedule
All meetings are held on the first Thursday of the month alternating between MGH and DFCI
from
5:30 PM to 7:00 PM

September 4, 2003	MGH – Cox 8	Ronny Drapkin
October 2, 2003	DFCI – Dana 1635	Esther Oliva
November 6, 2003	MGH- Cox 8	Sanja Sale and Bin Ye
December 4, 20003	DFCI- Dana 1635	Zhan Yong and Alex Ng
2004		
January 8, 2004	MGH – Cox 8	Akila Viswanathan and Alan D'Andrea
February 5	DFCI – TBA	Tayyaba Hasan and Lawrence Zukerberg
March 4	MGH – Cox 8	Daniel Cramer
April 1	DFCI – TBA	David Livingston
May 6	MGH - Cox 8	Pat Donahoe and Bo Rueda
June 3	DFCI – TBA	Annekathryn Goodman

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CANCER INSTITUTE

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February 12, 2004

Michael V. Seiden, M.D., Ph.D.
Assistant Professor of Medicine
Massachusetts General Hospital Cancer Services
Barbara and Melvin Nessel Cancer Services
Gillette Center for Women's Cancers
Cox 640, 100 Blossom Street
Boston, MA 02114-2617

RE: Ovarian Cancer Training Program at the DFHCC; DOD grant- OC020137
Ronny Drapkin, M.D., Ph.D., grant awardee
Project Title: In vivo and in situ molecular probing of developing ovarian cancer

Dear Michael,

Is it my pleasure to provide you with an update on Dr. Drapkin's progress during the past six month training period. Ronny was awarded a training grant from the Ovarian Cancer Training Program at the DFHCC (effective July 1, 2003) to facilitate his transition to an independent investigator. I meet with Ronny at least twice per week to review his progress and outline of future goals. I have encouraged him to pursue his ideas, establish collaborations, and publish his ongoing work. Ronny has been productive in all these areas, and I am delighted with his progress.

As you know, Ronny is an unusually talented physician-scientist and a fully trained pathologist. He is also an accomplished biochemist, having received his PhD from UMDNJ in the Howard Hughes laboratory of Danny Reinberg, a leading expert in he biochemistry of gene expression. Ronny has committed himself to the study of ovarian pathogenesis, and his particular interest is in understanding the molecular steps that underlie progression by ovarian surface epithelium from a wholly normal state to an invasive, neoplastic one.

Ronny outlined two major objectives in his grant proposal. The first was aimed at identifying and validating disease-related RNA and protein overexpression events that are characteristic of cells that have entered a pathway culminating in fully invasive ovarian carcinoma and not of normal surface epithelium. Ronny has made significant progress in this area. He first identified five genes (Mucin 1, Ep-CAM, CD9, Mesothelin, and HE4) that are over-expressed at the RNA level in the majority of ovarian carcinomas studied. Then, using a combination of commercially available antibodies and antibodies that he produced in the lab, Ronny demonstrated that all five gene products are over-expressed in the most common ovarian carcinomas (serous and endometrioid). Interestingly, during these studies, Ronny made an interesting observation. He noted that while all these markers are over-expressed in neoplastic cells and not in normal ovarian surface epithelium, they were over-expressed in ovarian surface epithelial cells that had undergone Mullerian metaplasia within cortical inclusion cysts. This suggested that the acquisition of ëtumorí markers requires a metaplastic transformation of the ovarian surface epithelium that is most readily seen in cortical inclusion cysts. This supports the unproven hypothesis that ovarian carcinomas arise within cortical inclusion cysts rather than de novo from

the surface epithelium and suggests that Mullerian metaplasia is a prerequisite for subsequent neoplastic transformation. Ronny, together with his colleagues at the BWH, recently submitted these results for publication.

During the course of these studies, Ronny discovered that HE4 is a protein secreted into the extracellular medium by ovarian cancer cells (and not by benign ovarian surface epithelial cells). This observation led him to ask whether HE4 might also be secreted into the bloodstream of patients with ovarian cancer. To address this possibility, he forged a fruitful collaboration with Drs. Patrick Sluss and Steve Skates at MGH, to develop a sensitive immunoradiometric assay for the detection of HE4 in the serum of patients with ovarian cancer. His preliminary results indicate that HE4 does indeed circulate in the bloodstream of these patients. Ronny is now actively trying to develop a monoclonal antibody against HE4 to ëupgradeí his assay for further clinical studies. An ELISA type assay will greatly facilitate the study of larger cohorts. He has, with you help, already identified and collected a set of cases with pre- and post-operative serum samples to test with his improved assay. Ronny is currently preparing a manuscript detailing the preliminary characterization of HE4 and hopes to submit it for publication shortly. I anticipate that, once he has a working , clinical-grade ELISA assay, he will be able to ascertain whether HE4 is a biomarker with clinical utility.

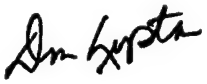
The second objective of his grant proposal was aimed at developing an in vivo system to study the pathogenesis of ovarian cancer. Ronny has been using a BRCA1 -/-, p53+/- murine model that develops both mammary and ovarian carcinomas. While attempts to demonstrate over-expression of the aforementioned markers in murine ovarian carcinomas by immunohistochemistry failed, using RT-PCR Ronny was able to detect the over-expression of HE4 and Mucin 1 in these tumors. Since the goal is to ultimately use the promoter of murine HE4 (or Mucin 1) as the catalyst for generating light emitting ovarian carcinoma cells, Ronny is actively working at defining and cloning the murine HE4 promoter. The linkage of the HE4 promoter to a luciferase-coding unit may well offer an opportunity to utilize whole animal luciferase-driven light emission technology to track early disease development in affected ovarian tissue. The goal of this approach, which offers the potential for highly sensitive detection of foci containing less than 10,000 ovarian neoplastic cells in the ovaries of living animals, is to detect elements of early disease in ovarian tissue using a non-invasive technique. Upon its detection, one could surgically remove an affected ovary for subsequent biological and molecular analysis. Such an approach offers the potential to gain insight into key early steps in the pathogenesis of the disease, an area that has been especially difficult to approach either in patients or an animal model.

In addition to the above studies, Ronny has been intimately involved in the characterization of a BRCA1-associated protein, called BACH1, which participates with BRCA1 in breast and ovarian cancer tumor suppression. Together with his colleague, Sharon Cantor, Ronny was able to demonstrate that clonal BACH1, synthesized in insect cells, is an enzyme that can perform the DNA-dependent ATPase and helicase functions that were predicted by its primary sequence. Indeed, before Ronny went to work on the problem, we had failed to detect an enzymatic function for the protein (as is not infrequently the case for certain proteins bearing helicase motifs). It was Ronnyís meticulous experimental approach to the problem that broke the ice. Subsequently, he demonstrated that two different germline sequence alterations in young women with very early onset breast and ovarian cancer render the helicase activity of BACH1 defective. Thus, we have now identified two individuals with wildtype BRCA genes, early onset breast and ovarian cancer, and defective BACH1 genes, further supporting the hypothesis that BACH1 is the product of a tumor suppressor gene. The results of these studies are in press at PNAS with Ronny as co-first author. One of Ronnyís ongoing efforts is to dissect out the molecular mechanism by which BACH1 contributes to BRCA1-mediated repair of double strand breaks. He recently submitted an NIH K08 application to fund these studies.

During his time in my laboratory, Ronny has successfully mentored two students and a technician. He has demonstrated a clear ability to effectively communicate and coordinate his teamsí efforts, in large part due to the fact that he is one of the most decent, generous, and good-humored people with whom I have ever had the privilege of working with. When he completes his training, I know that he will seek a post as an independent faculty member in a distinguished academic department where he can initiate his own research program in cancer biology. In this endeavor, I will support him fully and enthusiastically.

Ronny is a first rate young scientist with major potential for high order success in independent ovarian cancer research- his chosen field. I believe that continued support from the DFHCC Ovarian Cancer Research Training grant will help to insure a successful transition to full independence for Ronny.

Sincerely yours,



David M. Livingston, M.D.
Emil Frei Professor of Genetics and Medicine
Harvard Medical School; and, Deputy Director
Dana-Farber/Harvard Cancer Center

Mentor's Evaluation of Trainee

Period covered by this report:
July 1, 2003 – March 31, 2004

Trainee Name and Department Affiliation:
Dr. Sanja Sale
Department of Cell Biology
Harvard Medical School

Brief Project Description:

Title: PI3K/Akt, mTOR/S6K/eIF4E and Ras/MAPK/RSK signaling in three-dimensional epithelial ovarian cancer model system.

Dr. Sale's initial goal is to examine the regulation of several signaling pathways in malignant ovarian cancer cells (cell lines and tumor cells) in tissue culture to determine if there are any obvious differences in the regulation of these pathways. For example, is the Ras pathway up-regulated (monitored with ERK and/or RSK enzyme assays and activation-specific phosphospecific antibodies), is the PI3-kinase pathway upregulated (monitored with Akt enzyme assays and activation-specific phosphospecific antibodies), and is the mTOR pathway activated (monitored with S6K1 enzyme assays and activation-specific phosphospecific antibodies or phosphoS6 antibodies)? The importance of these pathways with regards to cell proliferation and survival will be examine through the use of pathway specific inhibitors (UO126 for the Ras/MAPK pathway, LY294002/wortmannin for the PI3-kinase pathway and rapamycin for the mTOR pathway) and RNA interference approaches.

The second major goal will be to establish a 3D organotypic ovarian cancer model system to determine if the same pathways are engaged and the importance of these pathways in proliferation and survival of the organoids.

Finally, based on the findings from the first two aims, cells with specific pathways knocked-down with stable expression of RNAi retroviruses will be characterized with regards to growth and survival in a mouse tumorigenesis model system to be completed in collaboration with Dr. Sandra Orsulic.

Your Role as a mentor for candidate's research:

My role as Sanja's mentor is to ensure that she is well trained in all basic aspects of signal transduction research with regards to cell biology, molecular biology and biochemistry technologies and knowledge. Furthermore, it is important that she develop a solid foundation in these areas so that she will be able to creatively and thoughtfully pose significant and important questions regarding carcinogenesis, come up with sound experimental design, and be able to effectively evaluate and interpret all experimental

results. This training, combined with her clinical and medical experience, should promote Sanja's development into a biomedical research scientist who is capable of easily bridging the gap between basic and clinical research.

Frequency of interactions and meetings with trainee:
Dr. Sale is free to meet with me on a regular basis.

Please provide your assessment of candidate's progress and plans in each of the following four areas:

1) Formal coursework and laboratory-based training.
   Sanja already possesses many of the basic lab techniques necessary to complete her lab work. She has been trained by members of my lab on the basics of signaling biochemistry and cell biology.

2) Research project: productivity, abstracts or publications, innovation
   Sanja works very hard and is already generating interesting new data. I anticipate that a paper will be submitted within 6 months.

3) Development of collaborations, and ability to communicate effectively
   Sanja communicates effectively with others in my lab (8 postdocs and 4 graduate students). She is also establishing an important collaboration with Dr. Sandra Orsulic, who will help her with the analysis of knock-down cells in a mouse tumorigenesis assay. These collaborations are an important part of her training.

4) Progress toward independence: understanding of field, creative thinking, ability to supervise support personnel, readiness to seek independent funding.
   Although only in my laboratory for one year, Sanja's progress has been good. Another year of experience and hard work will likely provide her with the tools she needs to begin her search for an independent position.

Do you recommend a major change in any aspect of the trainee's program (mentorship, didactic coursework, project)?

I do not recommend any major changes in Dr. Sale's present research directions.

Appendix 3
Mentor's Evaluation of Trainee
February 18, 2004

Period Covered by this Report: August 2003 - present

Trainee: Yong Zhan, PhD
Pediatric Surgical Research Laboratories
Massachusetts General Hospital

From: Patricia K. Donahoe, M.D.
Director, Pediatric Surgical Research Laboratories
Chief, Pediatric Surgical Services Emeritus

1. 1. Identification of the type I receptors and SMADS involved in Mullerian Inhibiting Substance (MIS) downstream at the time of Mullerian duct regression in rats and mice.

Dr. Zhan has innovatively used a number of SiRNAs in organ culture to knock down expression of type I receptor and SMAD genes and followed changes by *in situ* hybridization to determine which genes are functional in response to MIS. He found that Alk2 is functional in the rat, whereas Alk3 is the important type I receptor in Mullerian duct regression in the mouse. He also defined Smad 8 as the critical receptor SMAD in this pathway. Whereas others have used SiRNA in cell culture, it has only once been done in organ culture of salivary glands. Dr. Zhan adapted the technique used by Yamada et al, at NCI for use in organ cultures of embryonic urogenital ridge. Others in the laboratory had learned this technique from him in order to study branching morphogenesis in the lung and to identify genes involved in early ovarian differentiation. SiRNAs can knock down single genes, but also multiple genes, whose combined function could only be assessed by homologous recombination and cross breeding to explore redundant interactions.

2. Structure/functions studies of MIS

Dr. Zhan has also used his molecular skills to study structure of MIS. He created mutations in the MIS gene in order to produce secreted proteins suitable for crystallography of the MIS-C terminus. The first mutation required elimination of a secondary cleavage at position 229 which was producing a protein of 22kDa which was contaminating the 25kDa MIS-C terminus. He has also deleted a disordered region of the MIS gene, similar to one in BMP 7 that prevented its crystallography. He has combined the mutants to produce a single modified MIS-C terminus which is now being scaled up for expression and purification for use in crystallography trials.

3. Proteomics in the developing embryo

Dr. Zhan is exploring proteomic changes induced by MIS during Mullerian duct regression in the embryo. This work is also innovative since deuterium labeling followed by two dimensional mass spectroscopy has not previously been used on whole tissues. He is comparing simultaneous proteomic and genomic changes under the confluence of MIS then will do a systems analysis for "pathway" changes induced by MIS. We have done a microarray to screen for gene differences in MIS treated vs. nontreated OVCAR 8 human ovarian cancer cells. He is working together with BJ Renaud, another fellow in the laboratory, to confirm expression of candidate proteins modulated by MIS.

4. The "stem cell" nature of the coelomic epithelium

Dr. Zhan and I are working together to define the stem cell nature of the coelomic epithelium covering the embryonic urogenital ridge and the ovary. These studies will be an exciting part of the subsequent year for which we plan to collaborate with Niels Geijsen who has just been recruited as a new faculty member in Stem Cell and Regenerative Medicine.

As mentor, I help Yong to design experimental protocols, trouble shoot and interpret results and data, and assist him in presenting seminars and writing manuscripts. We work together on microdissections and RNAi experiments to define the critical timing of experiments and to interpret the results in embryos and in cell cultures. We interact at least three or four times a week, both informally at the bench and in formal laboratory meetings. He presents his material to me every other week in small laboratory groups and at formal laboratory meetings every six weeks, and to the gynecologic oncology group once or twice per year. For the future, we will train Dr. Zhan to use the "Sequencher" program to help interpret serial overlapping sequences, looking for gene mutations in patients with premenopausal ovarian cancer. He will also develop additional bioinformatic skills. Most of his training has been laboratory-based in the Pediatric Surgical Research Laboratories where David MacLaughlin and I act as his primary mentors. Our collaborators, Leo Bonilla at Thermo Electron and Thilo Stehle in Structural Biology, have been great contributors to his training program.

His creative work in RNAi in organ culture is being prepared for publication in either Genes and Development or Developmental Biology. Whereas others in the laboratory have attempted to employ this technology, Dr. Zhan has actually gotten it to work. He is hesitant in developing collaborations. His communicative skills need a great deal of work but he is improving steadily. We will spend a good deal of this year writing papers and proposals and I will seek his help in renewing one of our large R01's. He certainly understands concepts, is creative in experimental design, and has a good capacity for work, besides being a kind and sharing colleague. He is being assigned a student, and has worked very closely with one of our senior technicians. Given Dr. Zhan's progress over the past year, I expect leaps for him over the ensuing year.